

**REMARKS**

Claims 1-14 are pending. The Examiner has offered the following two grounds of rejection:

- I. Claims 1-14 are rejected under 35 U.S.C. 112 ¶1 for lack of enablement.
- II. Claims 1-14 are rejected under 35 U.S.C. 103(a) as allegedly obvious in light of Eibl ('984 patent) in view of Muguruma *et al.* and further in view of Eibl (Acta Pediat).

**I. The Claims Are Enabled**

The Examiner rejects Claims 1-14 under 35 U.S.C. § 112 ¶1 due to the belief that the specification only enables avian anti-TNF antibodies. *Office Action* pg. 2. The Examiner's assertion that the Applicants' specification contains a lack of guidance and would require undue experimentation in preparing anti-TNF antibodies from any species is not justified. In fact, the Applicants contemplated that anti-TNF antibodies can be produced in many species:

It is not intended that the present invention be limited to a particular type of antibody. ... Such antibodies may be made in a variety of animals [e.g., rabbits, horses, cows (e.g. in the milk) and birds]. The present invention also contemplates human and "humanized" antibodies. *Applicants' Specification* pg 6 ln 13-17.

Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended the Claim 1 & 9 to recite a "purified avian" anti-TNF antibody (See Example I for specification support). As a result of this amendment, Claim 6 is canceled and the dependency of Claim 7 is amended to recite Claim 1. This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

**I. The Claims Are Not *Prima Facie* Obvious**

Claims 1-14 are rejected under 35 U.S.C. 103(a) as allegedly obvious in light of Eibl II ('984 patent) in view of Muguruma *et al.*, and further in view of Eibl I (Acta Pediat). Applicants respectfully disagree.

**A. The Examiner Ignores The Three Prongs Of *Prima Facie* Obviousness**

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A *Prima Facie* Case Of Obviousness. The Examiner is reminded that if ONLY ONE of the above requirements is not met, then a *prima facie* case of obviousness does not exist. The Applicants submit that the Examiner's rejection does not meet these criterion. The Applicants rebut the establishment of a *prima facie* case of obviousness by the argument below.

**1. The References Do Not Teach Anti-TNF Antibodies**

The Examiner has offered Eibl II as the primary reference. The Examiner freely admits that Eibl II does not teach anti-TNF antibodies: "Eibl fails to specifically use anti-TNF antibodies in treating NEC." *Office Action* pg 5. Further, Eibl II: i) implicitly rules out any direct antibody inhibition of the cytokine<sup>1</sup>; ii) teaches IgA preparation by plasma fractionation (not by TNF immunization); and iii) presents no evidence that such human plasma IgA reacts with TNF. As a primary reference, Eibl II has no relevancy to the Applicants' claimed embodiment.

When asserting a combination of references to support an obviousness rejection (as the Examiner does here) the secondary and tertiary references are expected to supply the

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<sup>1</sup> "The decrease ... was due to a true down-modulation of the release of certain cytokines and not due to inhibition of cytokine detection." *Eibl II*, Example IV col 11.

deficiency(ies) of the primary reference. The Examiner has offered Muguruma *et al.* as a secondary reference, but again admits that Muguruma *et al.* does not teach anti-TNF antibodies: "Muguruma *et al.*, however, fails to specifically teach the use of antibodies ..." *Office Action* pg. 6. Clearly, Muguruma *et al.* is of no help to the Examiner to fill the deficiency of Eibl II.

Finally, the Examiner has offered Eibl I as a tertiary reference teaching crude plasma preparations of IgA-IgG but fails to establish any teaching regarding anti-TNF antibodies. *Office Action* pg. 6. Clearly, Eibl I is of no help to the Examiner to fill the deficiency of Eibl II (not surprising since these references are by the same research team and teach the same protocols).

The Examiner has attempted to find the missing claim limitation by using hindsight reasoning<sup>2</sup> and conclusory logic instead of facts:

A rejection based on section 103 clearly must rest on a factual basis, and these facts must be interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, all facts must be considered. The Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because it may doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis.

*In re Warner*, 379 F.2d 1011, 154 USPQ 173 (CCPA 1967). The Examiner attempts to argue that hindsight reconstruction using an Applicants' specification is proper by citing *McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). *Office Action* pg. 7-8. Such a reliance is not warranted in the present rejection. The Examiner is "gleaning knowledge **only from** the Applicants' disclosure" by asserting the obviousness of an anti-TNF antibody for the treatment of NEC. Nothing in the references provided by the Examiner describe a factual description of anti-TNF antibodies for NEC treatment as does the Applicants' specification (*supra*).

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<sup>2</sup> The Applicants incorporate by reference their arguments regarding hindsight reasoning elaborated in the previous two office action response.

The Applicants argue that the Examiner has failed to make a *prima facie* case of obviousness because when the Examiner's combination of Eibl II, Muguruma *et al.* and Eibl I, when viewed as a whole, suffer from a common lack of any facts regarding a teaching for the use anti-TNF antibodies in the treatment of NEC.

## **2. The References Do Not Teach Reasonable Success**

The Examiner attempts to establish this prong of *prima facie* obviousness case by stating:

The ordinary skill in the art would have had a reasonable expectation of success in employing anti-TNF for treating NEC, because it is well established that TNF potentiates the progress of NEC and **thus**, reducing the effects of TNF activity among human infants would improve or alleviate the pathological changes that would lead to NEC. Examiner states that any degree of relief from NEC would read on the scope of the instant claims, and the ordinary skill in the art would have had a reasonable expectation of success in at least observing some symptomatic relief when administering the anti-TNF taught by Eibl.

*Office Action* pg 6-7 [emphasis added]. At the outset, the Applicants reiterate that the Examiner's statement that Eibl teaches NEC treatment by anti-TNF is erroneous (*supra*). Further, the Federal Circuit requires any reference asserted for an "expectation of success" to explicitly predict that the recited claims will work. *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). Consequently, it is the Examiner who is making the conclusion that "reducing the effects of TNF activity among human infants would improve or alleviate ... NEC", **not** "one having ordinary skill in the art". As asserted above, the Examiner is continuing to speculate without a factual basis.

## **3. The References Provide No Motivation To Combine**

The Examiner believes one of skill in the art would be motivated to combine the cited references because the references:

... not only teach[] the use of anti-TNF antibodies for treatment of an inflammatory condition, but also makes clear that TNF plays an integral role in the progress of NEC (see all the secondary references). Therefore, one of ordinary skill in the art would have been motivated to use such antibodies to treat any other disease potentiated by TNF as the inflammatory mediator. NEC is one of such diseases.

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*Office Action* pg. 7. As detailed above, the Examiner's belief that the cited references teach the use of anti-TNF antibodies for treatment of NEC is simply wrong. The Examiner has pointed to no statement in any reference that suggests an antibody raised to a TNF antigen would be useful to treat NEC. The Examiner's assumption that an unstimulated crude fractionated IgA-IgG plasma preparation is equivalent to anti-TNF antibody (as described in the Applicants' specification) demonstrates a basic misunderstanding of the Applicants' claimed embodiment.

The Applicants conclude, therefore, that the Examiner cannot point to any statement in the combination of Eibl II, Muguruma *et al.* and Eibl I that suggests or motivates one skilled in the art to generate an anti-TNF antibody to treat NEC. Instead, the Examiner presupposes to be "one skilled in the art" and makes the following unsupported leap of logic:

Accordingly, even though Eibl II does not explicitly disclose the use of anti-TNF antibodies in treating NEC in neonates, it would have been obvious to one of ordinary skill in the art ... because as suggested by Muguruma and Eibl I and Wolf.

*Office Action* pg. 6. The Examiner is reminded of the Federal Circuit law discussed in both previous Office Action responses establishing that an Examiner is not one skilled in the art and, therefore, cannot make conclusory statements such as the one above without reference to specific *evidence* put forth by "one skilled in the art" (Applicants herein incorporate these arguments by reference).<sup>3</sup> The Examiner's statement that Muguruma, Eibl I and Wolf "suggest" anti-TNF antibodies is refuted by either the Examiner's own admissions (*supra*) or the reference's own teaching<sup>4</sup>.

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<sup>3</sup> *In re Rouffet*, *In re Rijckaert* and *In re Dembicczak*.

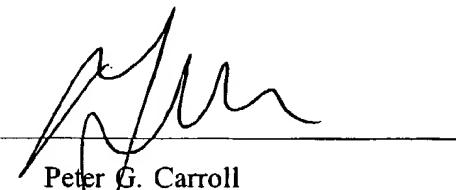
<sup>4</sup> Wolf (Acta Pediatr. Suppl) teaches only the use of IGABULIN (see page 38, right column, bottom). This is not an anti-TNF antibody.

**CONCLUSION**

Applicants believe that the arguments set forth above traverse the Examiner's rejections and therefore request that these grounds for rejection be withdrawn for the reasons set forth above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (617)-984-0616.

Date 3/31/2004

By



Peter G. Carroll  
Reg. No. 32,837

Medlen & Carroll, LLP  
101 Howard Street, Suite 305  
San Francisco, California 94105